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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,816	01/23/2001	Suzy Charbit	H7708-002	1320

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I.P. Docketing
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EXAMINER
BAHAR, MOJDEH

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 12/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/768,816	Applicant(s) CHARBIT ET AL.	
	Examiner Mojdeh Bahar	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *15-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response to the first office action of May 7, 2002, terminal disclaimer, and the declaration under 37 CFR 1.132 submitted September 17, 2002 are acknowledged. Applicant's terminal disclaimer has overcome the provisional obviousness double patenting rejection in the previous office action.

Claims 1-14 are herein examined on the merits.

Applicant's remarks regarding the restriction of claims 15-23 have been considered, but are not persuasive. As set forth in the previous office action, the second set of claims add a second pharmaceutical agent (as set forth in claims 15-22) to the originally presented compositions employed in the method claims herein. These second actives have a different function (i.e., symptomatic relief) and a different mode of operation than diacerein and rhein.

This application contains claims 15-23 drawn to an invention non-elected with traverse in Paper No. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Objections

The amendment filed April 18, 2001 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "pulmonary fibrosis".

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. "Pulmonary fibrosis" is not specifically described in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8 and 10-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Di Napoli WO 01/51044 A2 (US-PG-PUB 20020243057).

Di Napoli WO 01/51044 A2 (equivalent of US-PG-PUB 20020243057) discloses the employment of diacerhein and rhein in a method of treating psoriatic arthritis, see abstract. Di Napoli also teaches that both diacerhein and rhein are known to be useful in treating RA and OA, see page 4, lines 18-22. Di Napoli also teaches that diacerhein and rhein are known to inhibit IL1 and TNF-alpha production, see page 4, lines 24-29. Di Napoli finally teaches an oral dosage form of 100 mg and also teaches 50 mg capsules of diacerein, see page 16, lines 1-5 and claims 6-9.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martel-Pelletier et al. in view of Marcolongo et al. and applicant's admissions on page 1 of the specification.

Martel-Pelletier et al. discloses a method of treating osteo-arthritis (OA) employing diacerhein and its active metabolite rhein both of which are known to inhibit IL-1 beta synthesis and consequently have a beneficial affect on OA, see particularly abstract and page 754 col.1.

Martel-Pelletier et al. does not teach the amount of diacerhein to be administered or the dosage form, neither does it teach the treatment of other inflammatory or autoimmune diseases.

Marcolongo et al. teaches a method of treating osteo-arthritis comprising administering 50 mg of diacerhein per day in tablet form.

On page one of the specification applicant enumerates some pathological conditions characterized by an increases IL-1 and/or TNF-alpha level: rheumatoid arthritis, psoriatic arthritis, Wegener's disease, etc., see page 1 of the specification.

It would have been obvious to one of ordinary skill at the time the invention was made to administer the amounts of diacerhein taught in Marcolongo et al. in Martel-Pelletier et al.'s method of treating osteoarthritis and to employ a capsule as the dosage form for the composition.

It would have also been obvious to employ diacerhein in a method of treating rheumatoid arthritis, psoriatic arthritis, Wegener's disease, etc.

One of ordinary skill in the art would have been motivated to employ the amount of diacerhein taught in Marcolongo et al. in Martel-Pelletier et al.'s method of treating osteoarthritis because this amount is known to be useful in a method of treating osteo-arthritis, an inflammatory disease. Moreover the administration of a known active in a known dosage form, i.e. capsule is within the purview of the skilled artisan. Furthermore one of ordinary skill in the art would have been motivated to employ diacerhein, which is known to inhibit the synthesis of IL-1 beta, in a method of treating diseases characterized by an increases IL-1 and/or TNF-alpha level: rheumatoid arthritis, psoriatic arthritis, Wegener's disease, etc., and reasonably expect similar therapeutic effects.

Response to Arguments

Applicant's arguments filed September 17, 2002 regarding rejection of claim 3 under 35 USC 112 and the objection to the specification have been fully considered but they are not persuasive. Note that the original disclosure did not teach/claim the particular disorder of "pulmonary fibrosis." Moreover, the etiology of this disease is unknown, hence the name idiopathic pulmonary fibrosis. The term idiopathic means, a peculiar illness, of unknown cause, see Pulmonary Fibrosis Foundation reference enclosed herewith. Note also that in his arguments submitted January 23, 2002, applicant refers to Steadman's Medical Dictionary which in relevant part provide the following about Pulmonary Fibrosis: "**either completely idiopathic** or associated with collagen-vascular disease" see the ultimate paragraph of page 5 of the response.

Note also that the claims recite "method of treating **an underlying cause of a pathological condition**". Given that the **underlying cause** of pulmonary fibrosis is **uncertain** at best, "pulmonary fibrosis" is not supported by the original disclosure.

Dr. Provvedini's declaration submitted under 37 CFR 1.132 regarding the new matter rejection has been considered, but is not persuasive. Dr. Provvedini does not address the etiology of pulmonary fibrosis. Given that the claims are drawn to treating "underlying causes of the pathological condition" and that the declaration is silent as to the underlying cause of pulmonary fibrosis, the declaration does not overcome the new matter rejection.

Applicant's arguments filed September 17, 2002 regarding rejection under 35 USC 103 have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments and Dr. Provvedini's declaration regarding *in vitro* vs. *in vitvo* administration of diacerein have been considered, but are not persuasive. Applicant argues that Martel-Pelletier et al. discloses an *in vitro* testing of diacerein on cultured cartilage tissue, which is different from administering diacerein to a human patient. It is well known in the pharmaceutical art that the purpose of *in vitro* experimentation with pharmaceutical actives is to ultimately administer the active composition *in vivo* to an affected host/patient for some sort of therapy. This sort of *in vitro* testing is conventional in the pharmaceutical art. In fact, conventionally pre-clinical studies of pharmaceutical actives start *in vitro* in order to progress to

in vivo testing. Consequently, one of ordinary skill in the art would have reasonably believed that diacerein, which is known to inhibit the synthesis of IL-1 beta *in vitro*, would be useful in a method of treating diseases characterized by an increases IL-1 and/or TNF-alpha level. Given the results of the *in vitro* testing coupled with the suggestion that *in vivo* clinical studies of diacerein in arthritic patients are being done would provide the skilled artisan with a reasonable expectation of success to employ diacerein in a method of treating diseases characterized by an increases IL-1 and/or TNF-alpha level. Moreover, note that Marcolongo et al. teaches the *in vivo* administration of diacerein in arthritic patients. Therefore both *in vivo* and *in vitro* administration of diacerein are taught by the prior art.

Applicant argues that Marcolongo et al. does not teach that "diacerein will stop or delay cartilage destruction." Note that none of the claims herein recite such limitation and arguments as to unclaimed limitations are moot.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mojdeh Bahar whose telephone number is (703) 305-1007. The examiner can normally be reached on (703) 305-1007 from Monday to Friday from 9:00 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Mojdeh Bahar
Patent Examiner
November 29, 2002

SREENI PADMANABHAN
PRIMARY EXAMINER

12/1/02